#16 1/5/01 Election

PATENT
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Washington, D.C. 20231

On 27 July 2000

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Grey *et al.*

Application No.: 09/017,735

Filed: February 3, 1998

For: HLA-A2.1 BINDING PEPTIDES AND THEIR USES

Examiner: Ronald B. Schwadron

Art Unit: 1644

RESPONSE TO RESTRICTION REQUIREMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the Restriction Requirement mailed March 27, 2000, Applicants submit the Group election and election of species as detailed below with traverse. A petition to extend time for three months from March 27, 2000 to July 27, 2000 is submitted herewith.

The Examiner has set forth two Groups defined as follows:

Group I, claims 24, 25, 32, 33, 51, 52, 55, and 56, drawn to methods of gene therapy.

Group II, claims 9-23, 26-31, 34-50, 53, 54, and 57-62, drawn to methods of inducing a CTL response.

The Requirement for an Election of a Group is traversed. The two Groups set forth by the Examiner stem from a common concept and theory and are thus related.

Accordingly, prosecution of all of the claims of Groups I and II together would not place a substantially greater burden on the Examiner.

Restriction of an application is discretionary, as a restriction requirement is made only to avoid placing an undue examination burden on the Examiner and the PTO. Where claims can be examined together without undue burden, the Examiner must examine the claims on the merits even though they are directed to independent and distinct inventions (MPEP § 803). In establishing that an "undue burden" would exist for co-examination of claims, the Examiner must show that examination of the claims would involve substantially different prior art searches, making the co-examination burdensome. Applicants submit that examination of the claims of Group II would not involve a substantially different prior art search than that required to examine all of the claims together. All of the claims relate to methods of inducing a CTL response using an immunogenic peptide comprising an epitope having a specified motif or residue pattern. Accordingly, a thorough search of the subject matter of the Group II claims, which is not restricted by the source of the peptide, overlaps with the subject matter of the Group I claims. Thus, it would not impose an undue burden to search the subject matter of all of the claims together.

Based on these considerations, Applicants respectfully request that the Examiner withdraw the Restriction Requirement and consider the claims of Groups I and II together.

Formal election

As a formal matter, applicants elect Group II, claims 9-23, 26-31, 34-50, 53, 54, and 57-62, drawn to methods of inducing a CTL response. The election is traversed for the reasons set forth above.

Election of Species

Overview

The pending claims are directed to methods of inducing an immune response comprising providing a peptide comprising an epitope which comprises a structural motif

associated with peptide binding to HLA-A2.1 molecules. The Examiner has required election of a single species through multiple layers of restriction. The elections are traversed.

In order to facilitate an evaluation of the requirements set forth in Paper 12, a representative generic claim, for example claim 9, is presented below:

> 9. A method of inducing an immune response with a peptide comprising an epitope consisting of about 8-11 residues that will bind to an HLA-A2.1 molecule and induce an HLA-A2.1-restricted cytotoxic T cell response, said method comprising steps of:
>
> providing a peptide comprising a putative T cell epitope, said putative epitope comprising a structural motif associated with peptide binding to HLA-A2.1, said structural motif comprising a first anchor amino acid at position two from an N-terminus of the epitope, said first anchor selected from the group consisting of V, A, and T, and a second anchor amino acid selected from the group consisting of L, I, V, M and A at a carboxyl-terminus of the epitope, said peptide connected to another molecule to create a compound with a proviso that neither said peptide, said another molecule nor said compound comprise an entire native antigen;
>
> complexing the provided peptide, or a fragment thereof which comprises the epitope, with an HLA molecule; and,
>
> contacting a cytotoxic T lymphocyte (CTL) with the complex, whereby a CTL response is induced.

To be discussed in more detail below, Applicants submit that the multi-layered species election set forth in Paper 12 disregards key aspects of the invention and does not provide for examination of the invention as disclosed and claimed by the Applicants. Although some type of species election may be reasonable under the circumstances, the election requirements of Paper 12 are not. A reasonable species election should be based on the invention as disclosed and as claimed by the Applicants in the generic claims. Accordingly, any species election should focus on the elements provided in those claims, which relate to methods that recite a peptide with an HLA class I motif pattern of amino acid residues that bind a specified HLA molecule. Any appropriate species are delineated by one or more patterns defined by the motif set out in the claims. Accordingly, Applicants propose that an appropriate species election should be directed to species encompassed by a specific amino acid at a position two of an epitope together with the collective examination of the amino acid

residues that have been defined for the motif at the C-terminus of an epitope. Moreover, the proposed election does not present an undue burden for the Examiner.

Lastly, the species election requirement as set forth in Paper 12 is confusing. It does not apprise the Applicants how examination of the claims will proceed once an initial species is selected and is determined to be free of the prior art, nor does it enlighten the Applicants as to the strategies that might be employed to make elections. The Applicants thus have no assurance that the invention as they have disclosed and claimed it will be examined.

Discussion

The election of species detailed in Paper 12 requires the Applicants to elect a representative from the extensive list of the following criteria:

a.) a method that recites a peptide that comprises an epitope consisting of 8, 9, 10, or 11 residues; and

b.) a method that recites a peptide that is encompassed by a particular formula recited in the claims, i.e., a particular combination of residues at position 2 and the C-terminal end, and a peptide from one of the peptides recited in Table 3-5 that is encompassed by the elected motif formula; and

c.) a method that recites a peptide comprising an immunogenic epitope not linked to another molecule, a peptide attached to a lipid, a peptide attached to a T helper epitope, a peptide attached to a Pan DR epitope, a peptide attached to a CTL epitope , or a peptide linked to a carrier; and

d.) a method that recites a peptide encoding a cancer-associated antigen or a pathogen-derived peptide; and

e.) a method that recites a peptide isolated from a natural source or a chemically synthesize peptide; and

f.) an *in vivo* method or an *in vitro* method.

Applicants respectfully submit that the detailed dissection of the claimed subject matter is not justified. The species election requires that Applicants make choices that are directed to mere characteristics of embodiments and detract from the actual invention, *i.e.*, methods of inducing a CTL response using immunogenic peptides comprising epitopes defined

by a motif, intended by Applicants to be the focus of their application as properly claimed by the Applicants in their independent claims. A less onerous species election could have been required, and no unduly extensive and burdensome search would be necessary (MPEP § 808.01(a)). Accordingly, as will be explained, the claims should be examined as a whole or in a far less dissected manner.

A. The multi-layered election of species is confusing.

Applicants find the species election extremely confusing. The Applicants have not been able to ascertain how the Examiner will proceed with the examination of the application upon a determination that an initially elected "species" that conforms to all of the election requirements is free of the prior art. Will the determination of the next species to be examined be made based on the sequence of the epitope, the length of the epitope, the antigen from which the epitope is derived, or whether the epitope is linked to another molecule, *etc.*? This presents a major concern to the Applicants because they are not able to ascertain basic parameters of the examination and thus determine a suitable prosecution strategy. Furthermore, each time a new species is selected, various aspects of the invention are omitted at what seems to be an arbitrary choice of the Examiner (discussed in Section B., below). Under the traversed requirement of Paper 12, the ultimate nature of the invention thus appears to be defined not by the Applicants, but by the Examiner. Hence, it is evident that implementation of the species election requirements imposed by the Examiner would cause the loss of Applicants' right to pursue their invention as claimed and, thus, should be withdrawn.

B. Examination of a single species with multiple levels of characteristics conforming to the election requirements disregards important aspects of the invention as claimed.

It is improper for the Office to refuse to examine that which applicants regard as their invention (MPEP § 803.02, relating to Markush claims). Though the subject restriction requirement is for a species election which does not *per se* preclude examination of the scope of the generic claims in this application, the multi-layered species election could have undue and harsh consequences. The dissection of the claims in the manner of the Office Action could potentially prolong prosecution by directing focus to less critical characteristics that may not

even be significant elements of the actual invention. For example, where a method that recites a particular peptide is examined, the "motif" aspect of the invention is not being examined. The motif is a key aspect of Applicants' invention as reflected by the generic independent claims. "[T]he scope of subject matter of an invention is governed not by the examiner's conception of the invention, but by that which the applicant regards as his invention" *In re Wolfrum* 179 USPQ 620 (C.C.P.A. 1973) (addressing a 35 U.S.C. § 112 rejection).

Thus, Applicants maintain that requiring election among numerous characteristics set forth in Paper 12 ignores critical aspects of the invention as disclosed and claimed in the generic claims, such as claim 9 provided above. The generic claims relate to a method of inducing an immune response using immunogenic peptides that are conceptually bound together by a commonality of function, operation and effect. An immunogenic peptide recited in the claimes comprises an epitope *having a specified motif or residue pattern in a peptide,* wherein the peptide induces a cytotoxic T cell response in the context of an HLA A2.1 molecule and an HLA A2.1-restricted T cell. Thus, Applicants' invention is truly generic in that it covers motif patterns present in any peptide sequence that can be bound by HLA-A2.1 molecules and thereafter induce HLA-A2.1-restricted T cells, and is appropriately examined on a generic level. The claimed invention is not a method that recites a listing of unrelated sequences and is not in any way constrained by parameters such as antigenic source, other sequences to which it may be linked, or length of an HLA Class I epitope (as discussed in detail at a recent Examiner interview with Examiners Schwartz, Chan, Schwadron and for former Examiner Cunningham). Consequently, the dissection of the invention by the multi-layered election requirement loses sight of the actual invention and is tantamount to a recharacterization of the invention.

The generic claims in this case focus on methods of inducing an immune response that recite amino acid motif patterns present in immunogenic peptides comprising epitopes. Accordingly, Applicants propose that it would be appropriate to make a species election requirement based on the elements provided in the generic claim, namely of species defined by one or more motif patterns, in accordance with MPEP § 803.02. A species election consonant with MPEP policies would involve election of individual species as follows: a species encompassed by a specific amino acid at residue two (V, A, or T at position two)

together with the amino acid residues that have been defined for the motif at a C-terminus of an epitope (L, I, V, M, or A, at one of positions 8, 9, 10, or 11). Examination of the motif in this manner provides for not more than 60 species. (A discussion of proper species groupings is found in Section C., below). Thus, this proposed species election requirement is properly directed to the motif aspect of the invention set forth by the generic claims and focuses on the invention as a whole. This proposed election is not Applicants preferred choice; it is still somewhat problematic in that it yields results that are inconsistent with other PTO policies. This issue is discussed in detail in the following section.

C. Examination based on species election can yield results that are incongruous with other Patent Office policies.

(1) Applicants respectfully point out that the examination of claims in the pending application based on the species election set forth in Paper 12 or that proposed in the previous section can yield results that are incongruous with the policy set forth in the MPEP at § 803.04. Although MPEP § 803.04 is directed to nucleic acids and the claims of the present application are directed to methods of inducing an immune response that recite motif-bearing peptides, the same principles are at issue: the species election requirement could result in the examination of a fewer number of recited sequences that are actually related than if the claims were such that they fell within the policies of MPEP § 803.04 and the recited sequences were completely unrelated.

MPEP § 803.04 indicates that up to 10 independent and distinct, *i.e.*, completely unrelated nucleic acid sequences, can be co-examined in a single application. Therefore, Applicants would be entitled to the examination of up to 10 unrelated embodiments as disclosed and claimed by the Applicants. Thus, relative to the current claims, Applicants would be entitled to examination of embodiments that recite a position two with a defined residue and *up to 10* residues at a C-terminal position of an epitope, *e.g.*, C-terminal position 8, 9, 10, or 11. However, the number of possible residues at the C-terminal is *only 5* and these motif embodiments *are related.*

D. No undue examination burden is imposed by examining all C-terminal positions together.

For a given motif, no undue examination burden is imposed by examining one of V, A, or T at position two and L, I, V, M, or A residue at each of positions 8, 9, 10, and 11, i.e., the C- terminus of HLA class I epitopes. Computer searching techniques readily permit the searching of sequences representing designated amino acids at positions of choice. Such a search is not unduly extensive, but is thorough and properly includes the relevant motif species of a residue at a position two and up to 10 residues at any C terminal position. Moreover, for teachings related to peptides that bind to HLA class I molecules, it is prudent to consider C-terminal positions of epitopes which are 8, 9, 10, or 11 residues long, to get a truly comprehensive view of this art. Logic dictates that a typical computer search of the claimed motif would necessarily reveal any art related to peptides that are of different lengths. Moreover, the search would reveal that HLA class I motif technology is not tied to any particular antigen, whether a cancer-associated antigen or a pathogenic agent.

An example of a species conforming to a "motif-based" election requirement is an epitope possessing one of the three residues specified at position two (V, A, or T). That residue, in conjunction with any of the defined residues L, I, V, M, or A at the C-terminus of the epitope, is the motif. This approach leads to not more than 3 species of the invention. Examination of any one of these three species, *i.e.*, an epitope comprising: (i) residue V, with any of the defined C-terminal residues; (ii) residue A with any of the defined C-terminal residues; or (iii.) residue T with any of the defined C-terminal residues, properly focuses the prosecution of the application on the specified motif or residue pattern of the immunogenic peptide that induces a cytotoxic T cell response. Thus, election of any one of these three species results in examination of the invention in its totality as disclosed and claimed in the generic claims, and further, includes all of the specific embodiments set forth in all of the claims.

The species election detailed in the Paper 12 results in a division of Applicants' actual invention into an artificially voluminous and unreasonable number of "species" or more accurately, characteristics. An election requirement that defines a species as a method that recites a peptide comprising an epitope characterized by a motif pattern constitutes a "reasonable number" of species for examination, and thereby balances the rights of the

inventor and the administrative concerns of the Patent Office. An appropriate number of species, as discussed above, is: (i) 60, *i.e.*, a defined residue (V, A, or T) at position two of an epitope in combination with each residue (L, I, V, M, or A) at a C-terminal position of an epitope of 8, 9, 10, or 11 in length; or (ii) more appropriately 15, *i.e.*, a defined residue at position two and each residue defined for the C-terminal position of an epitope; or (iii) most appropriately 3, *i.e.*, a defined residue at position two and all of the residues defined for the C-terminal position of an epitope.

E. Election

As a formal matter, Applicants elect the following species with the understanding that upon the determination that the elected species is free of the prior art, additional species will be examined in accordance with MPEP § 803.02, which states that "should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended." and that "The prior art search will be extended to the extent necessary to determine the patentability of the Markush-type claim."

Accordingly, Applicants elect a method that recites:

a peptide that comprises an epitope consisting of 10 residues;

a peptide with a conserved residue at the second position from the N-terminus wherein the amino acid is A and a second conserved residue at the C-terminus wherein the amino acid is M;

the peptide MASDFNLPPV (SEQ ID NO:84);

a peptide attached to a CTL epitope;

a pathogen-derived peptide;

a chemically synthesized peptide; and

an *in vivo* method.

All of the species elections are made with traverse for the reasons set forth herein. The pending claims that read on the elected species are 9, 11-14, 16, 17, 21, 26, 28, 29, 30, 31, 34, 36-41, 43-47, 49, 50, 53, 54, 57, and 59-62.